

Increased Risk of Malignant Mesothelioma of the Pleura after Residential or Domestic Exposure to Asbestos: A Case–Control Study in Casale Monferrato, Italy

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The association of malignant mesothelioma (MM) and nonoccupational asbestos exposure is currently debated. Our study investigates environmental and domestic asbestos exposure in the city where the largest Italian asbestos cement (AC) factory was located. This population-based case–control study included pleural MM (histologically diagnosed) incidents in the area in 1987–1993, matched by age and sex to two controls (four if younger than 60). Diagnoses were confirmed by a panel of five pathologists. We interviewed 102 cases and 273 controls in 1993–1995, out of 116 and 330 eligible subjects. Information was checked and completed on the basis of factory and Town Office files. We adjusted analyses for occupational exposure in the AC industry. In the town there were no other relevant industrial sources of asbestos exposure. Twenty-three cases and 20 controls lived with an AC worker [odds ratio (OR) = 4.5; 95% confidence interval (CI), 1.8–11.1]. The risk was higher for the offspring of AC workers (OR = 7.4; 95% CI, 1.9–28.1). Subjects attending grammar school in Casale also showed an increased risk (OR = 3.3; 95% CI, 1.4–7.7). Living in Casale was associated with a very high risk (after selecting out AC workers: OR = 20.6; 95% CI, 6.2–68.6), with spatial trend with increasing distance from the AC factory. The present work confirms the association of environmental asbestos exposure and pleural MM, controlling for other sources of asbestos exposure, and suggests that environmental exposure caused a greater risk than domestic exposure. **Key words:** asbestos, asbestos cement, environmental exposure, pleural mesothelioma. *Environ Health Perspect* 109:915–919 (2001). [Online 23 August 2001]

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Malignant mesothelioma (MM) is associated with all types of asbestos, with higher risk for amphiboles (1). Beyond the well-known association with occupational exposure (2), an increased risk was found for domestic exposure (3,4) as well as for residence near asbestos factories (3) and mines (5,6). Epidemics of MM also occurred near naturally occurring deposits of asbestiform fibers and their use in whitewash and stucco (7–10).

Evidence relating MM to environmental (nonoccupational) exposure to asbestos, however, was not considered convincing in a recent review (11). Further information is expected from epidemiologic studies in areas where the risk from different sources of asbestos exposure can be disentangled and compared. One of these areas is Casale Monferrato (northwest Italy), a medium-size town where a large Eternit asbestos cement (AC) factory had been active from 1907 to 1985. Our original studies on mortality of workers (12) have been expanded to their wives (13) as well as to estimates of the incidence of MM in the general population (14). Rates were up to 10 times higher than those in other industrial areas of Northern Italy served by a cancer registry.

A case–control study conducted in 1995–1997 in several areas in Italy (including

Casale), Spain, and Switzerland was the first to estimate the risks for MM from nonoccupational asbestos exposure (15). Here we present the results of another study in the area of Casale, performed independently of the previous one and based on more individual data than was feasible in the international project. There is no overlapping between the present database and that used in the previous study.

Materials and Methods

The factory and the town. The size of the work force varied over time and never exceeded 1,500 workers. In 1981 the company reported the use of 15,000 tons of asbestos (10% crocidolite) (12). The factory is upwind from the town, at about 1,500 m from the center and 250 m from the closest residential areas. Its products were used largely in Casale. Environmental asbestos concentration was measured only shortly before the factory shutdown and afterward. Estimates reported here are the average of repeated measurements and, if not otherwise specified, are limited to airborne asbestos fibers (AF) with length > 5 μ m and diameter > 0.3 μ m. Marconi et al. (16) in 1984 reported between 11 AF/L close to the plant and 1 AF/L in the city area farthest away. The Local Health Authority (LHA) in

1990–1991 measured annual averages below 1 AF/L, this concentration being exceeded in 12% of samples (17). Chiappino et al. (18) reported a range of 2.2–7.4 AF/L in the residential areas of Casale—more than in 7 other Italian cities. Amphiboles in the three sets of estimates ranged between 15% and 50% of AF. In Casale average concentration of total (any length) asbestos fibers was 48.4 AF/L and of total amphiboles was 1.5 AF/L, versus, respectively, 0.2–12.1 and 0.0–0.2 AF/L in other industrial cities (18,19). Besides AC production and activities related to it (warehousing and transportation of raw asbestos and final products), no other noticeable sources of asbestos exposure of industrial origin were recorded in Casale (20).

Study design. This is a population-based case–control study that includes cases of pleural MM recorded between 1 January 1987 and 30 June 1993 in residents in the Local Health Authority (LHA) of Casale (48 towns and 100,000 inhabitants, of whom 40,000 live in Casale). Cases were retrospectively identified through periodic surveys of the pathology units of the hospitals serving the study area (14).

Cases were histologically diagnosed and revised by a panel of five pathologists

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(21,22). Each pathologist independently reviewed the slides and classified each case according to an ordinal scale (definite, probable, possible, improbable, and definitely not MM) (23). Cases were included if all pathologists rated them at least as "possible" and none as "improbable" or "definitely non-MM." Ninety percent of all submitted cases were accepted. Seven cases for which slides could not be traced were included.

Cases and controls were individually matched by sex, birth date (± 18 month), vital status, and date of death (± 6 months). Controls were randomly selected either from the files of residents in the LHA of Casale (if the corresponding case was alive) or from the mortality files (for deceased cases, no cause of death was excluded). Living status of cases was checked before the sampling of controls. Three cases alive at sampling were matched to alive controls but died before the interview; the original controls were not replaced. To increase power in the younger age classes, the case-control ratio was 1:2 for cases 60 years or older and 1:4 for younger cases.

Trained interviewers conducted the interviews from 1993 to 1995 using a standardized questionnaire. When the index subject had died, the closest relative was interviewed. The questionnaire included sections on demographic characteristics, smoking, radiation treatments, schools attended, lifelong occupational and residential histories, as well as occupations held by spouse, parents, and other cohabitants. Information on residence included the address and a description of each dwelling and its neighborhood environment. Indoor (i.e., domestic) exposure to asbestos was addressed through questions on the use of asbestos material such as ironing table; fire-proof sheets close to heat sources such as cookers, ovens, fireplaces, and stoves; AC material in very close proximity to the house (e.g., garden, courtyard); or AC roofs in the courtyard or very close to the house. Some questions about domestic exposure to asbestos were added after inclusion of the first 24 cases and 80 controls.

Interview data were checked against other sources of information. For example, occupational histories (subjects and relatives) were compared to factory rosters. Cohen's kappa (24) of ≥ 0.78 was estimated for work at the AC factory of the index subject (five subjects with discordant information), of the spouse (three subjects discordant), and of parents (seven subjects discordant). For subjects with discordant information, the questionnaire was used. Regarding residential history in Casale, the most precise available information from the questionnaire and the Town Office was used. All addresses of study subjects in Casale were coded as geographic

coordinates. Interview, retrieval of information from city files, coding, revision of questionnaires, and the like were conducted blindly in respect to case-control status.

Main data analyses used conditional logistic regression (25,26). OR_C (conditional logistic regression) indicates the logistic regression estimate and is computed taking into account the matched sets. Statistical significance is set at 0.05.

Occupational exposure in the AC industry corresponds to a very high intensity of exposure and could obscure the effect of indicators of less intense exposure. Therefore, results are presented either adjusted by occupation in the AC industry (included in the model) or, if there was effect modification, stratified or limited to subjects without occupational exposure.

To analyze residential and occupational exposure together, we computed a composed variable with mutually exclusive values (upper level for the subjects who ever worked in the AC industry; intermediate levels for subjects who ever lived in Casale, classified according to the residence closest to the factory; and lower levels for residents in other towns of LHA). Each subject was rated according to his or her occupational history and dwelling closest to the AC factory. The last 20 years before the date of diagnosis (or,

if controls, before the date of diagnosis of the corresponding case) were ignored. The categories used for classifying dwellings in the town of Casale correspond to different sections of the town: The stratum "less than 500 m from the factory" includes the factory neighborhood; the city center is cut in two halves by the 1,499 m radius and the rest of the town is almost entirely included in the 2,499 m radius; greater distances include only small neighborhoods in almost rural setting.

Results

One hundred sixteen cases and 330 controls were eligible for the study, and 102 (89%) and 273 (83%) were interviewed. After the exclusion of matched sets with either the case or all controls missing, 102 sets (345 subjects) remained available for conditional regression analyses. Results are given including only the 345 subjects included in the latter. There were no significant differences in age, sex, or residence between respondents and nonrespondents.

Table 1 describes the complete data set of 375 interviewed subjects. Cases and controls presented similar distributions by age, sex, and distribution among interviewers. Average duration of the interview was similar for cases and controls, both overall and

Table 1. Descriptive information on the subjects included in case-control study on malignant mesothelioma of the pleura in Casale Monferrato, Italy.

| Subjects | Cases | | Controls | |
|--|-----------------|---------|-----------------|---------|
| | No. | Percent | No. | Percent |
| Sex | | | | |
| Men | 60 | 58.8 | 167 | 61.1 |
| Women | 42 | 41.2 | 106 | 38.8 |
| Age (mean \pm SD) | 65.3 \pm 11.9 | | 65.3 \pm 11.8 | |
| Interviewer | | | | |
| A | 25 | 24.5 | 83 | 30.4 |
| B | 77 | 75.5 | 190 | 69.6 |
| Duration of the interview (minutes, mean \pm SD) | 40.9 \pm 14.7 | | 40.9 \pm 14.3 | |
| Vital status | | | | |
| Dead | 95 | 93.1 | 252 | 92.3 |
| Alive | 7 | 6.9 | 21 | 7.7 |

Table 2. Case-control study on malignant mesothelioma of the pleura in Casale Monferrato, Italy. Analysis of the risk of mesothelioma by occupation.

| Occupation | Cases | | Controls | | Crude | | Adjusted for AC industry | |
|------------------------|-------|---------|----------|---------|--------|----------|--------------------------|---------|
| | No. | Percent | No. | Percent | OR_C | 95% CI | OR_C | 95% CI |
| Industry | | | | | | | | |
| Asbestos cement | 27 | 26.5 | 13 | 5.4 | 7.3 | 3.2–16.4 | | |
| Agriculture | 33 | 32.4 | 120 | 29.4 | 0.4 | 0.3–0.8 | 0.4 | 0.2–0.8 |
| Metal industry | 11 | 10.8 | 33 | 13.6 | 0.7 | 0.3–1.5 | 0.8 | 0.3–1.8 |
| Construction | 8 | 7.8 | 33 | 13.6 | 0.6 | 0.3–1.4 | 0.6 | 0.2–1.4 |
| Brickworks | 10 | 9.8 | 20 | 8.2 | 1.4 | 0.6–3.1 | 1.5 | 0.6–3.6 |
| Garment and textile | 15 | 14.7 | 19 | 7.8 | 1.8 | 0.9–3.9 | 2.1 | 0.9–4.6 |
| Occupation | | | | | | | | |
| Electrician | 5 | 4.9 | 9 | 3.7 | 1.5 | 0.4–4.8 | 1.5 | 0.4–5.4 |
| Bricklayer and related | 8 | 7.8 | 32 | 13.2 | 0.6 | 0.3–1.4 | 0.6 | 0.2–1.4 |

The analyses were conducted using conditional regression and were limited to job categories with at least five cases. Subjects are classified in respect to all occupations ever held and thus may appear in more than one category. For each category the reference is the group of the subjects never engaged in it.

by interviewer. Cases and controls did not differ significantly in number of jobs (on average 1.9 for cases and 1.8 for controls) and of residences (4.4 and 4.2); the frequency of missing data was also similar for cases and controls.

Results on occupational history are presented in Table 2, for job categories including at least five cases. Twenty-seven cases and 13 controls had ever worked in the AC industry. Among these, median latency was 39 years for cases and 36 for controls. For 2 (1 case, 1 control) and 6 (2 cases, 4 controls) the latent period was, respectively, shorter than 20 years and between 20 and 30 years (latency < 30: $OR_C = 6.1$; 95% CI, 1.4–26.3; ≥ 30 : $OR_C = 7.5$; 95% CI, 2.9–19.4). The garment industry was the only other site presenting an increase of the risk close to statistical significance. Of 15 cases and 19 controls engaged in this industry, six cases and four controls worked in a factory making artificial silk that was active in the 1940s (no information on work conditions was found); six cases and 10 controls worked as tailors and the remaining three and five worked in activities related to the garment industry. Agriculture entailed a significant reduction in risk, both in the total data set and in the subset of subjects who never worked in the AC industry (for the latter, $OR_C = 0.4$; 95% CI, 0.3–0.8, based on 21 cases).

Twenty-three cases and 20 controls reported domestic exposure through relatives working in the AC industry during cohabitation (Table 3). The highest risk was observed when either father or mother was employed in AC industry (one case and one control had both parents employed). Mutual adjustment by relatives' exposure status changed results only slightly, and we do not report these changes in detail. Four cases and 3

controls reported handling the working clothes of their relative (two and one also worked in the AC industry). Because there was evidence of interaction between relative's occupational exposure and index subject's occupational exposure, Table 3 presents also the results for the stratum of subjects not exposed in the AC industry. Among 27 cases and 13 controls employed in the AC industry, one and two had one parent exposed, two and five had the spouse, and five and three had other relatives exposed.

Table 4 shows results on domestic exposure from asbestos-containing items, based on the subset of 78 cases and 174 controls who responded to the full questionnaire (see "Methods"): OR_C was 1.5 (0.7–3.0) considering "any indoor and/or outdoor domestic exposure." ORs for individual items (ironing table, fireproof sheets, and so on) were in the range 0.6–2.5, none being statistically significant.

We observed a statistically significant increase in risk for those who attended their grammar school in Casale (in the subset of subjects that never worked in the AC industry: $OR_C = 3.3$; 95% CI, 1.4–7.7 based on five cases and 10 controls). Numbers were too small for separate estimation of risk according to school location.

Table 5 presents the analysis of occupational exposure and distance between the AC factory and the dwelling location (i.e., the dwelling closest to the AC factory where the subject lived for any length of time in any period of life before the last 20 years): ORs are well in excess of 1 and statistically significant at all distances from the factory, with some evidence of a spatial trend. OR_C for residence in Casale (at any distance from the factory) is 20.6 (95% CI, 6.2–68.6), after adjustment for occupation in the AC industry.

The main analyses were repeated after exclusion of the seven cases that were not submitted to histologic revision or the 28 lung cancer deaths from the control group. In both cases the results did not change.

Discussion

This study extends our previous investigations (12–14) on the causes of the dramatic epidemics of mesothelioma in Casale. It is also one of the largest studies on MM ever performed in a small area.

Several potential biases in the study design have been kept under control. Diagnostic criteria are reliable: With few exceptions, histologic slides were reviewed by a panel blinded to patient's exposures, and cases were accepted on the basis of stringent criteria. In Casale, thoracoscopy was the standard diagnostic procedure for pleural effusions, providing adequate bioptic samples (27). Results did not change after exclusion of unrevised cases.

Most interviews were double-blind; the interviewer was unaware of the disease status and the questionnaire was submitted to proxy respondents. Indicators of quality of interviews were identical for cases and controls. Participation rate was high for both. For some items, information obtained through questionnaires was validated against factory and municipality files, which provided additional information on residential histories.

As expected, exposure in the AC industry was a strong risk factor. The risk relative to the category "never employed in the AC industry" was remarkably lower than the corresponding estimate versus the category "subjects with neither occupational nor residential exposure," which highlights the need for a truly nonexposed category in occupational studies on risk factors present in both occupational and nonoccupational compartments of the environment.

The limited data on asbestos airborne concentration in the town suggest substantial exposure. Moreover, in postmortem material from the same area, 25 out of 31 subjects with no occupational exposure presented asbestos bodies (AB) in the lungs (6 with over 1,000 AB) (28).

Table 3. Risk of mesothelioma in relation to relatives' occupational exposure in the AC industry.

| Relatives | Cases | | Controls | | Crude | | No occupation in the AC industry | |
|----------------------|-------|---------|----------|---------|--------|----------|----------------------------------|----------|
| | No. | Percent | No. | Percent | OR_C | 95% CI | OR_C | 95% CI |
| Father and/or mother | 9 | 8.8 | 5 | 2.1 | 4.6 | 1.5–13.9 | 7.4 | 1.9–28.1 |
| Spouse | 6 | 5.9 | 8 | 3.3 | 1.5 | 0.5–4.5 | 3.1 | 0.6–17.7 |
| Other relatives | 13 | 12.8 | 11 | 4.5 | 3.7 | 1.4–9.5 | 3.4 | 1.0–11.8 |
| Any relatives | 23 | 22.6 | 20 | 8.2 | 3.3 | 1.6–6.5 | 4.5 | 1.8–11.1 |

OR_C was estimated with conditional logistic regression. For each category the reference is the group without relatives employed in the AC industry.

Table 4. Risk of mesothelioma in relation to domestic exposure to asbestos.

| Exposure | Cases | | Controls | | Crude | | Occupation in the AC industry | |
|---|-------|---------|----------|---------|--------|----------|-------------------------------|----------|
| | No. | Percent | No. | Percent | OR_C | 95% CI | OR_C | 95% CI |
| Any outdoor domestic exposure (asbestos material in the garden or courtyard, excluding roofs) | 11 | 14.9 | 15 | 8.9 | 1.6 | 0.7–4.0 | 1.3 | 0.4–3.5 |
| Any indoor domestic exposure (asbestos material inside the house) | 5 | 6.5 | 17 | 10.1 | 0.5 | 0.2–1.5 | 0.6 | 0.2–2.2 |
| Asbestos material on the ironing table | 4 | 5.2 | 2 | 1.2 | 2.3 | 0.4–14.4 | 2.5 | 0.3–19.1 |
| Asbestos cement sheets or roofs in the garden or courtyard | 46 | 59.0 | 77 | 45.3 | 1.7 | 0.9–3.1 | 1.8 | 0.9–3.6 |
| Any indoor or outdoor domestic exposure. | 49 | 62.8 | 88 | 51.8 | 1.5 | 0.8–2.9 | 1.5 | 0.7–3.0 |

OR_C was estimated with conditional logistic regression. For each category the reference is the group without either indoor or outdoor exposure.

The estimate of an increased risk for attendance to grammar schools located in an asbestos-polluted area is new and requires confirmation: It underlines the greater risk for exposure in childhood. The relevance of the latter is likely to increase as the generation born in the years with the largest asbestos use becomes older. Elsewhere we presented a case of environmental asbestosis in a female teacher of a school located close to the AC factory in Casale (28). That school was attended by three cases and four controls in the present study. Attempts to measure risk after this exposure were unsuccessful because of the overlap of occupational exposure in three cases and two controls.

ORs for residential exposure decreased with distance, but the risk remained high even at considerable distance from the factory; this suggests a role for sources of exposure other than atmospheric pollution from a point source. Known sources of exposure besides the AC plant include improper use of AC residuals, such as playgrounds made with AC residuals mixed into the soil to create hard pavement and improve water absorption. Some buildings have a layer of asbestos fibers (either AC residuals or even flock) in the loft for thermal insulation. Unfortunately, these reports are anecdotal; no quantification of the frequency of these sources of exposure has been made. Moreover, raw asbestos and AC materials were transported through the town to and from the railway station and nearby warehouse. Both railway station and warehouse are on the opposite side of the town from the factory. Our study could not consider mobility of subjects in the city, which would tend to average exposure from geographically defined sources.

A major problem in studies on environmental exposures is the reliability of exclusion of occupational exposures. Occupation in the AC industry was chosen as a proxy to occupational exposure because it is highly specific and can be reliably assessed with precision. Sensitivity may be lower. But in Casale other sources of occupational asbestos

exposure are limited in number and importance (20), and their spatial distribution is not associated with distance from the AC factory. Therefore, residual occupational exposure is not likely to confound the observed results.

The first evidence of risk of mesothelioma after domestic asbestos exposure was presented by Wagner (29). Subsequent reports highlighted the risk for spouses and offspring of asbestos workers (30–35). The relative risk of 3.1 for spouses in the present study lies in the confidence interval of a previous independent estimate in the same area [standardized mortality rate (SMR) = 792; 95% CI, 216–2,029] (13). Here, parent's work in the AC factory was a stronger risk factor (OR = 7.4, based on nine exposed cases). These estimates are consistent with those of other recent studies of cohabitants with asbestos workers. Spirtas et al. (36) observed an increase in risk 13-fold for men and 3-fold for women (pleural and peritoneal mesothelioma together; analyses ignored occupational exposure). Hansen et al. (5) found 11 cases of malignant mesothelioma in the 2,393 offspring of crocidolite miners in Wittenoom, Australia (risk was not estimated). In a case-control study in Northern England, Howel et al. (37) estimated an OR of 5.8 for para-occupational exposure (not better specified). In our previous international study (15), OR was 7.8 (95% CI, 1.7–36.2) for domestic exposure from cohabitation with an asbestos worker and handling of his/her work-clothes.

Residence close to a source of asbestos pollution was used as a proxy to environmental exposure in previous investigations. Newhouse and Thompson (30) observed a relative risk (RR) of 2.2 for subjects (11 cases, five controls) who ever lived within about 800 m from an asbestos factory. Schneider et al. (38) observed an association of MM with neighborhood asbestos exposure, limited to subjects living outside Hamburg. Howel et al. (37), in Northern England, reported a nonstatistically significant increase of risk after environmental exposure (OR = 2.3; 95% CI, 0.5–9.7), but the prevalence of

such exposure in nonoccupationally exposed subjects was very low. Among residents close to the crocidolite mine of Wittenoom, Hansen et al. (5) estimated an RR of $1.59 \times \log$ (fibers per milliliter) from environmental asbestos exposure; however, that study did not take into account domestic exposure, which involved most MM cases (12 wives and 11 children out of 27 cases). Camus et al. (6) observed seven cases of pleural cancer (SMR 763; 95% CI 306–1,573) among women residents in the chrysotile mining area of Quebec, but did not investigate their occupational history. In our international case-control study (15), risk increased parallel to the probability and intensity of environmental asbestos exposure: ORs for high and middle exposure categories (i.e., living at less than 500 m and at 500–2,000 m, respectively, from an asbestos industry) were 45.0 (95% CI, 6.4–318.0) and 9.5 (95% CI, 2.5–36.5). On the other hand, no increased risk related to the geographic proximity to a source of asbestos was observed by McDonald and McDonald (32) or by Teta et al. (39), and questionable results were obtained in the study by Hammond et al. (40).

Little is known about other risk factors for mesothelioma (4), and it is unlikely that they played an important role in present results. The hypothesis of a role of simian virus 40 (41) is hardly tenable because only 2.9% cases were born in the age cohort that was scheduled to receive the intramuscular polio vaccine in 1955–1963, when it was possibly infected by the virus.

Our present work confirms the association of environmental asbestos exposure and pleural MM, after careful control for other sources of asbestos exposure; and it suggests that in Casale, environmental exposure caused a greater risk than domestic exposure. This study was performed independently of our previous international study (15), thus strengthening our inferences. Finally, in our analyses, the plant producing AC was considered a point source of exposure. Most likely, however, exposure also originated from other sources, such as AC residuals improperly used in the town or transportation of raw

Table 5. Risk of mesothelioma in relation to residence in different municipalities in the LHA of Casale Monferrato.

| Subjects | Cases | | Controls | | OR _C | 95% CI |
|--|-------|---------|----------|---------|-----------------|------------|
| | No. | Percent | No. | Percent | | |
| Occupation in the AC industry | 27 | 26.5 | 13 | 5.4 | 52.5 | 12.5–220.0 |
| Ever lived in Casale, distance from the AC industry | | | | | | |
| < 500 m | 5 | 4.9 | 2 | 0.8 | 27.7 | 3.1–247.7 |
| 500–1,499 m | 41 | 40.2 | 52 | 21.4 | 22.0 | 6.3–76.5 |
| 1,500–2,499 m | 9 | 8.8 | 12 | 4.9 | 21.0 | 4.9–91.8 |
| > 2,500 m | 4 | 3.9 | 9 | 3.7 | 11.1 | 1.8–67.2 |
| Ever lived in any of the municipalities surrounding Casale | 12 | 11.8 | 42 | 17.3 | 8.3 | 2.1–32.6 |
| Never in any of the above-mentioned categories | 4 | 3.9 | 113 | 46.5 | 1 (Ref) | |
| Ever lived in Casale, any distance | 59 | 57.8 | 75 | 30.8 | 20.6 | 6.2–68.6 |

Ref, reference. Subjects are classified according to the distance from the AC industry of the residence closest to it. OR_C was estimated with conditional logistic regression. The model adjusts for the effect of the occupational exposure of the relatives.

asbestos and final products. It is now mandatory to study geographic determinants of risk with a distribution-free approach (42) as well, and to take advantage of study results to suggest the possible location of other sources of exposure and to indicate remedial actions.

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